

### Amendments to the Claims

1. (Withdrawn) A nucleic acid molecule comprising a P66<sup>shc</sup> coding sequence incorporating at least one mutation as compared to the wild type sequence or the sequence as shown in SEQ ID NO: 1 such that the protein encoded by the coding sequence has at least one serine residue absent or replaced by a different amino acid residue.
2. (Withdrawn) A nucleic acid molecule according to claim 1 wherein the serine residue is selected from the group consisting of S17, S19, S20, S26, S28, S36, S38, S40, S41, S54, S60, S66, S80 and S102.
3. (Withdrawn) A nucleic acid molecule according to claim 1 wherein the serine residue is selected from the group consisting of S28, S36 and S54.
4. (Withdrawn) A nucleic acid molecule according to claim 1 wherein the serine residue is S36 and is replaced by alanine (p66<sup>shc</sup>S36A).
5. (Withdrawn) A polypeptide encoded by a nucleic acid molecule according to claim 1.
6. (Withdrawn) A replicable vector comprising nucleic acid according to claim 1 operably linked to control sequences to direct its expression.

7. (Withdrawn) A host cell transformed with a vector according to claim 6.

8. (Withdrawn) A method of producing a modified p66<sup>shc</sup> polypeptide comprising culturing a host cell according to claim 7 so that the p66<sup>shc</sup> polypeptide is produced.

9. (Currently Amended) A method of modulating resistance in cells to oxidative stress by affecting the p66<sup>shc</sup> signal transduction pathway in a cell, said method comprising contacting said cell with an agent capable of modulating p66<sup>shc</sup> gene expression, wherein said contact modulates resistance in said cells to oxidative stress relative to untreated cells, and wherein said agent is an antisense nucleic acid molecule capable of hybridizing to a nucleic acid encoding SEQ ID NO: 2, thereby modulating resistance in said cells to oxidative stress.

10. (Previously presented) A method according to claim 9 wherein said agent reduces or prevents p66<sup>shc</sup> expression.

11. (Withdrawn) A method according to claim 9 wherein said agent is a vector comprising nucleic acid encoding p66<sup>shc</sup>, said vector being capable of incorporating said nucleic acid into the genome of the cell so that the nucleic acid encoding p66<sup>shc</sup> is expressed in the cell.

12. (Currently amended) A method of increasing resistance in cells to oxidative stress comprising the step of disrupting the p66<sup>shc</sup> signaling pathway via introduction of an antisense

nucleic acid molecule which hybridizes to a nucleic acid encoding SEQ ID NO: 2, thereby disrupting the p66<sup>shc</sup> signaling pathway, said disruption increasing resistance to oxidative stress in said cells.

13. (Withdrawn) A method according to claim 12 wherein said step of disrupting the p66<sup>shc</sup> affects the susceptibility of p66<sup>shc</sup> to phosphorylation.

14. (Withdrawn) A method according to claim 12 wherein said step of disrupting the p66<sup>shc</sup> pathway causes a mutant p66<sup>shc</sup> polypeptide to be expressed such that at least one serine residue present in the wild type p66<sup>shc</sup> is absent or replaced by a different amino acid residue.

15. (Withdrawn) A method according to claim 14 wherein said serine residue is S36 and is replaced by alanine.

16. (Withdrawn) A method according to claim 14 wherein said mutant polypeptide cannot be serine phosphorylated.

17. (Withdrawn) A method according to claim 12 wherein said disruption affects the ability of a serine/threonine kinase, p38 or MAPK to phosphorylate p66<sup>shc</sup>.

18. (Withdrawn) A method according to claim 12 wherein the step of disrupting the p66<sup>shc</sup> signaling pathway includes contacting the cell with an antibody binding domain capable of

specifically binding to the p66<sup>shc</sup> polypeptide such that its function is disrupted or prevented.

19. (Previously presented) A method according to claim 12 wherein said step of disrupting the p66<sup>shc</sup> signaling pathway includes disrupting the p66<sup>shc</sup> gene expression.

20. (Cancelled)

21. (Cancelled)

22. (Previously presented) A method for increasing cellular resistance to oxidative stress comprising administering an effective amount of an agent in a pharmaceutically acceptable carrier, wherein said agent disrupts p66<sup>shc</sup> expression or a step in the p66<sup>shc</sup> signaling pathway in a cell, wherein said agent is an antisense oligonucleotide capable of hybridizing to a p66<sup>shc</sup> nucleic acid encoding SEQ ID NO: 2, thereby increasing cellular resistance to oxidative stress.

23. (Cancelled)

24. (Previously presented) A method according to claim 22 wherein said antisense oligonucleotide is RNA.

25. (Cancelled)

26. (Withdrawn) A method according to claim 22, wherein said agent is an antibody binding domain capable of specifically binding to a p66<sup>shc</sup> polypeptide or fragment thereof.

27. (Previously presented) A method according to claim 22 wherein said agent is administered for the treatment of a disease selected from the group consisting of arteriosclerosis, ischemic heart disease, lung emphysema, myocardial infarction, stroke, premature aging, cell senescence, Parkinson's, Alzheimer's, cancers, and vascular complications of diabetes.

28. (Withdrawn) A method of increasing resistance to tumor formation in a tissue comprising the step of increasing the expression of p66<sup>shc</sup> in said tissue.

29. (Withdrawn) A method according to claim 28 wherein the step of increasing the expression of p66<sup>shc</sup> includes contacting the tissue with an agent capable of increasing expression of p66<sup>shc</sup> gene.

30. (Withdrawn) A method according to claim 29 wherein said agent is a transcription factor.

31. (Withdrawn) A method according to claim 29 wherein said agent is a vector comprising nucleic acid encoding p66<sup>shc</sup> polypeptide said vector being capable incorporating said nucleic acid into the genome the cells of the tissue.

32. (Withdrawn) A method of screening for compounds capable of modulating resistance in cells to oxidative stress by

modulating the p66<sup>shc</sup> signaling pathway comprising contacting a candidate compound with a p66<sup>shc</sup> expression system; determining the amount of a compound of the signaling pathway; and comparing said amount of the component with the amount of the component in the absence of said candidate compound.

33. (Withdrawn) A method according to claim 32 further comprising the step of preparing a pharmaceutical composition comprising the candidate compound capable of modulating a p66<sup>shc</sup> pathway and a pharmaceutical acceptable carrier.

34. (Withdrawn) A method according to claim 32 wherein said step of determining the amount of a compound of the signaling pathway is an enzyme activity assay.

35. (Withdrawn) A method according claim 32 wherein said candidate compounds include nucleic acid sequences, antibody binding domains, and protein nucleic acids.

36. (Currently Amended) A method of reducing intracellular levels of reactive oxygen species (ROS) in a cell, said method comprising the step of contacting said cell with an agent capable of inhibiting the expression of a p66<sup>shc</sup> polypeptide in said cell, wherein said agent is an antisense nucleic acid molecule capable of hybridizing to nucleic acid encoding SEQ ID NO: 2, thereby reducing intracellular levels of ROS.

37. (Previously presented) A method according to claim 36 wherein said contact with said nucleic acid reduces or prevents expression the p66<sup>shc</sup> polypeptide.

38. (Withdrawn) A method according to claim 36 wherein the agent is an antibody binding domain capable of specifically binding to the p66<sup>shc</sup> polypeptide such that its functions are inhibited or prevented.

Claims 39-41 (Canceled)

42. (Withdrawn) A method of determining the presence or absence of a p66<sup>shc</sup> nucleic acid or a mutant, variant derivative or allele thereof in a biological sample, comprising the step of contacting said sample with a nucleic acid molecule capable of hybridizing specifically with said p66<sup>shc</sup> nucleic acid or a mutant, variant derivative or allele thereof and determining whether or not hybridization has taken place.

43. (Withdrawn) A method of determining the presence or absence of a p66<sup>shc</sup> polypeptide or a mutant, variant derivative or allele thereof in a biological sample, comprising the step of contacting said sample with an antibody binding domain capable of binding p66<sup>shc</sup> or a mutant, variant derivative thereof and determining whether or not binding has taken place.

44. (Withdrawn) An expression system comprising a nucleic acid vector having a p66<sup>shc</sup> coding sequence or fragment thereof inserted therein.

45. (Withdrawn) A method according to claim 10 wherein said agent is a vector comprising nucleic acid encoding p66<sup>shc</sup>, which when expressed in a cell results in production of p66<sup>shc</sup>.

46. (Cancelled)

47. (Currently Amended) The method according to claim 9 46, wherein said antisense nucleic acid ~~oligonucleotide~~ is RNA.

Claims 48-51 (Cancelled)

52. (Previously presented) A method according to claim 9, wherein said agent is administered for the treatment of a disease selected from the group consisting of arteriosclerosis, ischemic heart disease, lung emphysema, myocardial infraction, stroke, premature aging, cell senescence, Parkinson's, Alzheimer's, cancer, and vascular complications of diabetes.